

25-Hydroxyvitamin D Concentrations and In Vivo Insulin Sensitivity and β -Cell Function Relative to Insulin Sensitivity in Black and White Youth

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OBJECTIVE—To examine the relationships between plasma 25-hydroxyvitamin D [25(OH)D] and in vivo insulin sensitivity and β -cell function relative to insulin sensitivity, disposition index (DI), in black and white youth.

RESEARCH DESIGN AND METHODS—Plasma 25(OH)D concentrations were analyzed in banked specimens in healthy youth aged 8 to 18 years who had existing data on hyperinsulinemic-euglycemic and hyperglycemic clamp to assess insulin sensitivity and secretion, and measurements of body composition, and abdominal visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT).

RESULTS—A total of 183 research volunteers (mean $\pm$ SD; age, 12.6 ± 2.2 years; 98 white, 98 male, 92 obese) were studied. Analysis of HbA_{1c}, fasting glucose and insulin, insulin sensitivity, and DI across quartiles of plasma 25(OH)D revealed no differences among whites. In blacks, the observed significance of higher insulin sensitivity and DI in the highest quartile of 25(OH)D disappeared after adjusting for any of the adiposity measures (BMI or fat mass or VAT or SAT). The difference in insulin sensitivity (9.4 ± 1.2 vs. 5.6 ± 0.5 mg/kg/min per μ U/mL; $P = 0.006$) between 25(OH)D nondeficient (≥ 20 ng/mL) versus deficient (< 20 ng/mL) black youth also was negated when adjusted for adiposity.

CONCLUSIONS—In healthy youth, plasma 25(OH)D concentrations bear no independent relationship to parameters of glucose homeostasis and in vivo insulin sensitivity and β -cell function relative to insulin sensitivity. It remains to be determined whether in youth with dysglycemia the relationships are different and whether vitamin D optimization enhances insulin sensitivity and β -cell function.

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Vitamin D is proposed to play a role in glucose homeostasis and β -cell function. In adults, low 25-hydroxyvitamin D [25(OH)D] concentration is found to be associated with higher risk of hyperglycemia (1), insulin resistance (2), and type 2 diabetes mellitus (3). In children, limited vitamin D data show an association with fasting

hyperglycemia in the nondiabetic range and fasting surrogate indices of insulin sensitivity (4,5). Animal data show impaired insulin secretion during vitamin D deficiency and improvement of insulin secretion with vitamin D supplementation (6,7). Actions of vitamin D on glucose homeostasis are postulated to be mediated by its autocrine and paracrine functions in the regulation of

transcription of genes in pancreatic β -cells, skeletal myocytes, and immune cells by improving insulin secretion and sensitivity and reducing inflammation (8).

Despite such publications, controversy remains regarding the relationship between 25(OH)D concentrations and insulin secretion (2,9) and insulin sensitivity (10–12). Most studies reporting an inverse association between 25(OH)D and insulin resistance in adults have relied on surrogate indices of insulin sensitivity derived from fasting glucose and insulin levels (8). The reported relationship between 25(OH)D and insulin secretion also varies among studies because of differences in participant characteristics and methods for assessment of insulin secretion (oral glucose tolerance test or meal challenge or surrogate indices derived from fasting glucose and insulin versus the gold-standard hyperglycemic clamp) (8). Adiposity is a determinant of 25(OH)D status and influences insulin secretion and sensitivity (8,13). However, most of the studies assessing 25(OH)D-glucose homeostasis relationships have used body mass index (BMI) as an indirect measure of adiposity for covariate adjustment and lack direct measures of body fat or body fat topography. Data remain limited in pediatrics, and to our knowledge, there are no published reports of assessing the relationship between 25(OH)D concentrations and clamp measured in vivo insulin sensitivity and secretion. We demonstrated previously an inverse relationship between adiposity measures and 25(OH)D concentrations in youth (13). Because adiposity is a strong determinant of insulin sensitivity and secretion, we examined the relationships between plasma 25(OH)D and in vivo insulin sensitivity and secretion, with the hyperinsulinemic-euglycemic and the hyperglycemic clamp, in children to test whether plasma 25(OH)D is associated with insulin sensitivity, and β -cell function relative to insulin sensitivity, disposition index (DI), independent of adiposity. Plasma 25(OH)D concentration was measured in

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banked specimens in youth who had existing data on hyperinsulinemic-euglycemic and hyperglycemic clamp, and measurements of body composition, and abdominal visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT).

RESEARCH DESIGN AND METHODS

Subjects

Study participants were 183 healthy prepubertal and pubertal (Tanner stage I–V), nonobese and obese black and white youth aged 8 to 18 years from Pittsburgh, PA (latitude: 40.4° North). None were taking any medications that influence glucose, blood pressure, or lipid metabolism. Subjects were participants in National Institutes of Health-funded “insulin resistance in childhood [K24]” and “childhood metabolic markers of adult morbidity in blacks [R01]” studies. Data from some of the participants were previously reported (13–15). Subjects were recruited through newspaper advertisements and fliers posted on university campus, youth recreational facilities, and bus routes. Studies were approved by the University of Pittsburgh Institutional Review Board. Signed parental informed consent and participant assent were obtained before participation.

Study design

Study procedures were completed at the Children’s Hospital of Pittsburgh National Institutes of Health-funded Pediatric Clinical and Translational Research Center (PCTRC). Subjects were comprehensively assessed at enrollment by medical history; physical examination, including Tanner staging of pubertal development; and routine hematological and biochemical testing. Weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, using a weighing balance and wall-mounted stadiometer. Age and sex-based BMI cutoffs were used for categorizing children as obese (≥ 95 th percentile). Racial categorization was based on parents’ self-identification of being black or white for at least three generations.

Clamp studies

A 3-h hyperinsulinemic-euglycemic (14,15) and 2-h hyperglycemic (15,16) clamp were performed in a random sequence within a 1- to 4-week period at the PCTRC in all participants ($n = 183$) after 10 to 12 h of overnight fasting as described before.

In vivo insulin sensitivity

A 3-h hyperinsulinemic-euglycemic clamp with crystalline insulin (Humulin; Lilly, Indianapolis, IN) was infused at a constant rate of 40 mU/m²/min in normal weight subjects and 80 mU/m²/min in obese subjects to suppress hepatic glucose production as before (14–17). Plasma glucose was clamped at 5.6 mmol/L with a variable rate infusion of 20% dextrose based on arterial plasma glucose determinations every 5 min.

In vivo insulin secretion

First- and second-phase insulin secretion was measured during a 2-h hyperglycemic clamp (15). Plasma glucose was rapidly raised to 12.5 mmol/L by a bolus infusion of 25% dextrose and maintained at that level by a variable rate infusion of 20% dextrose for 2 h.

Calculations

Insulin-stimulated glucose disposal was calculated using the average exogenous glucose infusion rate during the final 30 min of the 3-h hyperinsulinemic-euglycemic clamp as before (17). Insulin sensitivity was calculated by dividing the insulin-stimulated glucose disposal rate by steady-state plasma insulin concentrations, during the last 30 min of the clamp, multiplied by 100, to normalize the disposal rate for race and adiposity-related differences in insulin clearance and achieved insulin concentrations (16,17). First-phase insulin concentration was calculated as the mean of five determinations from 2.5 to 12.5 min, and second-phase insulin concentration was calculated as the mean of eight determinations from 15 to 120 min of the 2-h hyperglycemic clamp (16). DI was calculated as the product of insulin sensitivity and first-phase insulin concentration (15).

Body composition and abdominal fat distribution

Body composition (fat mass and percentage of body fat [%BF]) was assessed as described before (18) with dual-energy X-ray absorptiometry in all participants except eight whose weight exceeded the weight limit for the dual-energy X-ray absorptiometry table. Abdominal SAT and VAT were measured in 150 subjects by a 10-mm single axial computed tomography (CT) scan at L_{4–5} intervertebral space as reported previously (18) and in 26 subjects with magnetic resonance imaging (MRI) (19). CT or MRI data are missing in six subjects who exceeded the weight limit for CT or MRI.

Biochemical measurements

Plasma glucose was measured using a glucose analyzer (YSI, Yellow Springs, OH), and insulin concentrations were measured by radioimmunoassay (17). Hemoglobin A1C (HbA_{1c}) was measured by high performance liquid chromatography (Tosoh Medics). Plasma 25(OH)D was measured using competitive protein binding assay using vitamin D-binding protein as described by Chen et al. (20). The competitive protein-binding assay recognizes 25(OH)D₂ as well as it does for 25(OH)D₃, and thus this assay measures the total 25(OH)D in the circulation. The assay was validated by liquid chromatography tandem mass spectrophotometry assay, which measures separately 25(OH)D₂ and 25(OH)D₃ (21). The intrassay and interassay coefficients of variation were 8 ng/mL and 10 ng/mL, respectively. The lower limit of detection was 4 ng/mL.

Statistical analysis

Differences in age, adiposity measures, metabolic parameters, and plasma 25(OH)D between black and white subjects were examined using Student *t* test or Mann-Whitney *U* test depending on data distribution. Racial differences pertaining to categorical data (sex, pubertal status, season of assessment, proportion of obesity, and vitamin D status) were assessed using χ^2 . BMI percentile and %BF were log-transformed before comparative analysis. Within each race, subjects were divided into quartiles of plasma 25(OH)D concentrations (blacks [1st or lowest quartile: 5 to 11 ng/mL; 2nd quartile: 12 to 16 ng/mL; 3rd quartile: 17 to 20 ng/mL; 4th or highest quartile: 21 to 39 ng/mL]; whites [1st or lowest quartile: 5 to 18 ng/mL; 2nd quartile: 19 to 22 ng/mL; 3rd quartile: 23 to 27 ng/mL; 4th or highest quartile: 28 to 46 ng/mL]). Differences in clinical characteristics, body composition parameters, fasting glucose, fasting insulin, HbA_{1c}, first-phase insulin concentration, insulin sensitivity, and DI were examined across the 25(OH)D quartiles, in each race, by ANOVA with Bonferroni post hoc correction or Kruskal-Wallis test for quantitative variables depending on data distribution and χ^2 test or Fisher’s exact test for categorical variables. ANCOVA models adjusted for adiposity measures (BMI, fat mass, VAT, or SAT) were used to assess differences in insulin sensitivity and DI across 25(OH)D quartiles or between vitamin D-deficient versus nondeficient participants. Pearson or Spearman correlation depending on data distribution

were used to assess bivariate relationships between 25(OH)D and fasting glucose, fasting insulin, HbA_{1c}, insulin sensitivity, first-phase insulin, and DI. Partial correlation analysis was used to assess the association between insulin sensitivity and 25(OH)D adjusting for race and adiposity measurements in all participants. The independent effect of plasma 25(OH)D on insulin sensitivity, first-phase insulin, and DI was examined through multiple regression analysis, adjusting for age, race, pubertal status, season of assessment and sex, and any one of the adiposity measures (BMI or fat mass or VAT or SAT). In the model examining the independent effect of plasma 25(OH)D on insulin secretion further adjustments were also made for insulin sensitivity. No interactions were modeled. All statistical assumptions were met. Data are presented as mean $\pm$ SEM unless otherwise specified. Statistical significance was set at $P < 0.05$. The statistical analysis was done using PASW Statistics (version 18; SPSS, Chicago, IL).

RESULTS—A total of 183 healthy children (98 [54%] white, 98 [54%] male, 92 [50.3%] obese, 42 [23%] Tanner I, prepubertal) were studied either during winter/spring (81 [44.3%]) or summer/fall (102 [55.7%]). The study cohort had a mean ($\pm$ SD) age of 12.6 ± 2.2 years and a mean ($\pm$ SD) plasma 25(OH)D concentration of 20.1 ± 8.0 ng/mL. The demographic, body composition, metabolic profile, and vitamin D status data for all participants and the black versus white differences for these parameters are shown in Table 1. Whites were more often assessed during winter/spring and had higher amount of VAT than blacks. Consistent with our previous observations blacks had higher first-phase insulin and DI and lower plasma 25(OH)D concentrations and higher proportion of vitamin D deficiency than whites (13,17).

In all participants (blacks and whites combined), 25(OH)D correlated with insulin sensitivity ($r = 0.173$, $P = 0.019$), but this disappeared after adjusting for race and any of the adiposity measures (BMI or fat mass or VAT or SAT). There was no significant association between 25(OH)D and first-phase insulin ($r = -0.120$, $P = 0.107$) or DI ($r = -0.040$, $P = 0.595$).

Subjects' characteristics by race across 25(OH)D quartiles

In whites, there were no significant differences in age, pubertal status, season of assessment, proportion of obesity, BMI, BMI

Table 1—Participants' characteristics

	All participants	Whites	Blacks	P
n	183	98	85	
Age (years)	12.6 ± 0.2	12.8 ± 0.2	12.4 ± 0.2	NS
Sex (%)				
Male	98 (53.6)	52 (53.1)	46 (54.1)	NS
Female	85 (46.4)	46 (46.9)	39 (45.9)	
Puberty (%)				
Prepubertal	42 (23)	21 (21.4)	21 (24.7)	NS
Pubertal	141 (77)	77 (78.6)	64 (75.3)	
Season (%)				
Winter, Spring	81 (44.3)	46 (46.9)	29 (34.1)	0.010
Summer, Fall	102 (55.7)	52 (53.1)	56 (65.9)	
Obese (BMI ≥ 95) (%)				
Yes	92 (50.3)	44 (44.9)	48 (56.5)	NS
No	91 (49.7)	54 (55.1)	37 (43.5)	
Body composition				
BMI (kg/m ²)	26.7 ± 0.7	26.4 ± 0.9	27.1 ± 1.0	NS
BMI percentile (%)	78.6 ± 2.0	77.1 ± 2.8	80.3 ± 2.7	NS
Fat mass (kg)	22.4 ± 1.2	21.7 ± 1.7	23.0 ± 1.8	NS
%BF	30.8 ± 1.0	30.7 ± 1.3	31.0 ± 1.5	NS
VAT (cm ²)	44.4 ± 2.9	50.0 ± 4.2	38.0 ± 3.7	0.034
SAT (cm ²)	290.4 ± 18.0	294.0 ± 25.2	286.2 ± 26.0	NS
Metabolic profile				
Fasting glucose (mg/dL)	95.7 ± 0.4	96.4 ± 0.6	94.9 ± 0.6	NS
Fasting insulin (μ U/mL)	25.7 ± 1.2	26.7 ± 1.8	24.4 ± 1.4	NS
HbA _{1c} (%)	5.3 ± 0.04	5.2 ± 0.04	5.5 ± 0.1	<0.001
Insulin sensitivity (mg/kg/min per μ U/mL)	7.0 ± 0.4	7.3 ± 0.6	6.7 ± 0.5	NS
First-phase insulin (μ U/mL)	171.8 ± 10.3	138.2 ± 10.8	210.5 ± 17.4	<0.001
DI (mg/kg/min)	846.0 ± 54.0	645.4 ± 36.9	$1,077.2 \pm 103.0$	<0.001
Vitamin D status				
25(OH)D (ng/mL)	20.1 ± 0.6	23.2 ± 0.8	16.5 ± 0.7	<0.001
Deficient [25(OH)D <20 ng/mL] (%)	97 (53)	37 (37.8)	60 (70.6)	<0.001
Insufficient [25(OH)D 20 to <30 ng/mL] (%)	67 (36.6)	45 (45.9)	22 (25.9)	
Sufficient [25(OH)D ≥ 30 ng/mL] (%)	19 (10.4)	16 (16.3)	3 (3.5)	

Prepubertal, Tanner I; pubertal, Tanner II-V.

percentile, fat mass, %BF, SAT, and VAT across the plasma 25(OH)D quartiles.

In blacks, there were no differences in age, season of assessment, and proportion of obesity across the 25(OH)D quartiles. However, the proportion of pubertal and prepubertal children varied across the 25(OH)D quartiles ($P < 0.001$), with fewer pubertal youth in the highest quartile, consistent with our prior findings (13). BMI, BMI percentile, %BF, and SAT were significantly different across the plasma 25(OH)D quartiles. However, there were no differences in VAT across the quartiles. In post hoc comparisons, youth in the highest plasma 25(OH)D quartile had significantly lower BMI (21.7 ± 1.9 vs. 30.3 ± 1.9 kg/m², $P = 0.021$), BMI percentile (63.6 ± 6.8 vs.

93.2 ± 2.4 , $P = 0.010$), %BF (24.1 ± 3.5 vs. 36.7 ± 2.3 , $P = 0.040$), and SAT (142.9 ± 41 vs. 362.4 ± 48.9 cm², $P = 0.028$) than those in the second plasma 25(OH)D quartile.

Parameters of glucose metabolism by race across 25(OH)D quartiles

In whites, HbA_{1c}, fasting glucose, fasting insulin, insulin sensitivity, first-phase insulin, and DI were not different across the plasma 25(OH)D quartiles (Fig. 1).

In blacks, HbA_{1c}, fasting glucose, fasting insulin, and first-phase insulin secretion were not different across the plasma 25(OH)D quartiles. Insulin sensitivity and DI differed significantly across the plasma 25(OH)D quartiles; those in the highest 25

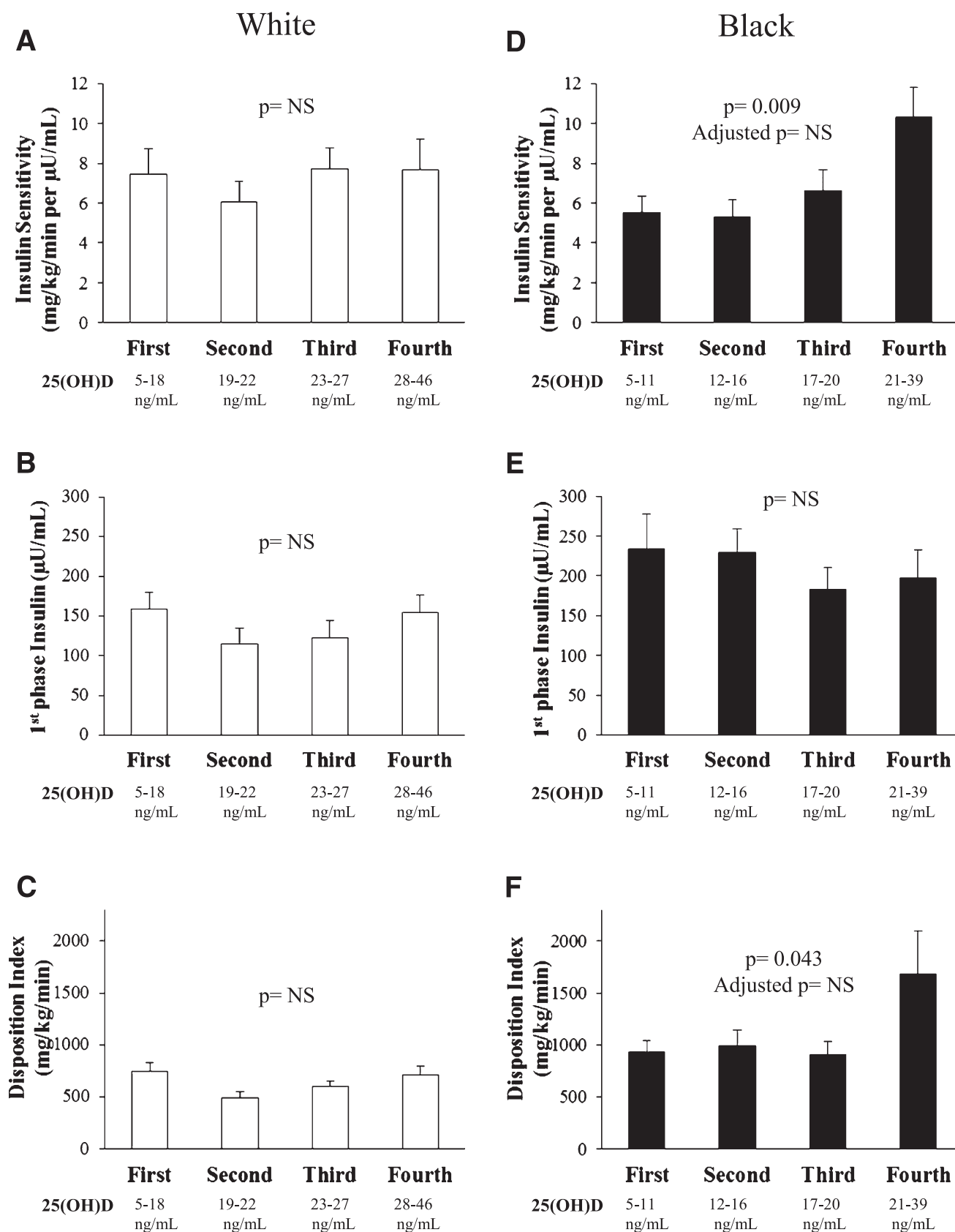


Figure 1—Insulin sensitivity, first-phase insulin, and DI by quartiles of plasma 25(OH)D in white (A–C, left) and black (D–F, right) youth before and after adjustment for any adiposity measure (BMI or fat mass or VAT or SAT).

(OH)D quartile had higher insulin sensitivity and DI than those in the lower three quartiles. However, these differences were no longer significant after adjusting for any of the adiposity measures (BMI, fat mass, SAT, or VAT) (Fig. 1).

Correlations of plasma 25(OH)D and parameters of glucose metabolism by race

Plasma 25(OH)D was positively associated with insulin sensitivity only in blacks ($r = 0.242$, $P = 0.026$). However, this association disappeared after adjusting for any of the adiposity indices (BMI, fat mass, SAT, or VAT). There were no significant associations between plasma 25(OH)D and first-phase insulin or DI in blacks or whites (data not shown).

Vitamin D status and differences in parameters of glucose metabolism by race

In whites, vitamin D–nondeficient [25(OH)D ≥ 20 ng/mL] versus deficient [25(OH)D < 20 ng/mL] youth did not differ in insulin sensitivity (7.3 ± 0.8 vs. 7.3 ± 1.1 mg/kg/min per $\mu\text{U/mL}$, $P = \text{NS}$) and DI (615.7 ± 40.4 vs. 694.5 ± 71.4 mg/kg/min, $P = \text{NS}$).

In blacks, insulin sensitivity was higher in vitamin D–nondeficient versus deficient youth (9.4 ± 1.2 vs. 5.6 ± 0.5 mg/kg/min per $\mu\text{U/mL}$, $P = 0.006$). However, this difference was no longer significant when adjusted for any of the adiposity indices (BMI, fat mass, VAT, or SAT). There was no significant difference in the first-phase insulin or DI between vitamin D–nondeficient versus –deficient blacks or whites.

Independent relationship of 25(OH)D and insulin sensitivity, first-phase insulin, and DI

In all participants combined, multiple linear regression analysis adjusting for age, race, pubertal status, season of assessment and sex, and any one of the adiposity measures (BMI or fat mass or VAT or SAT) showed no independent association of plasma 25(OH)D with insulin sensitivity, first-phase insulin, and DI. In blacks, who had shown higher insulin sensitivity and DI in the highest vitamin D quartile, 25(OH)D was not independently associated to insulin sensitivity or DI when adjusted for age, pubertal status, season of assessment and sex, and any one of the adiposity measures (BMI, fat mass, VAT, or SAT) (Table 2).

Table 2—Multiple linear regression analysis: independent effect of circulating 25(OH)D (by every 1 ng/mL) on insulin sensitivity, first-phase insulin secretion, and β -cell function relative to insulin sensitivity (DI) in all participants and on insulin sensitivity and DI in blacks

	B	95% CI	P
All participants (n = 183)			
Dependent variable: insulin sensitivity (mg/kg/min per $\mu\text{U/mL}$)			
Unadjusted	0.121	0.020–0.023	0.019
Adjusting for selected variables ¹ and BMI (kg/m ²)	–0.001	–0.067 to 0.064	0.901
Fat mass (kg)	0.004	–0.063 to 0.071	0.897
VAT (cm ²)	–0.016	–0.089 to 0.056	0.657
SAT (cm ²)	–0.007	–0.076 to 0.062	0.844
Dependent variable: first-phase insulin secretion ($\mu\text{U/mL}$)			
Unadjusted	–1.462	–3.990 to 1.067	0.256
Adjusting for selected variables ² and BMI (kg/m ²)	0.271	–2.148 to 2.691	0.825
Fat mass (kg)	0.172	–2.176 to 2.520	0.885
VAT (cm ²)	1.020	–1.214 to 3.253	0.369
SAT (cm ²)	0.965	–1.215 to 3.145	0.383
Dependent variable: DI (mg/kg/min)			
Unadjusted	–3.587	–16.893 to 9.719	0.595
Adjusting for selected variables ¹ and BMI (kg/m ²)	–0.234	–13.377 to 12.909	0.972
Fat mass (kg)	0.274	–13.342 to 13.890	0.968
VAT (cm ²)	–1.083	–14.897 to 12.730	0.877
SAT (cm ²)	–0.569	–14.288 to 13.151	0.935
Black participants (n = 85)			
Dependent variable: insulin sensitivity (mg/kg/min per $\mu\text{U/mL}$)			
Unadjusted	0.193	0.024–0.363	0.026
Adjusting for selected variables ³ and BMI (kg/m ²)	0.003	–0.088 to 0.094	0.940
Fat mass (kg)	0.017	–0.074 to 0.108	0.707
VAT (cm ²)	0.019	–0.100 to 0.137	0.753
SAT (cm ²)	–0.031	–0.133 to 0.070	0.538
Dependent variable: DI (mg/kg/min)			
Unadjusted	19.354	–13.272 to 51.981	0.241
Adjusting for selected variables ³ and BMI (kg/m ²)	0.215	–32.376 to 32.807	0.990
Fat mass (kg)	2.385	–30.489 to 35.258	0.886
VAT (cm ²)	4.024	–29.630 to 37.677	0.812
SAT (cm ²)	–0.340	–33.827 to 33.147	0.984

¹Age, race, puberty (Tanner stage), sex, season; ²age, race, puberty (Tanner stage), sex, season, insulin sensitivity (mg/kg/min per $\mu\text{U/mL}$); ³age, puberty (Tanner stage), sex, season.

CONCLUSIONS—In healthy black and white obese and nonobese youth aged 8 to 18 years, when examined together or separately, there were no independent relationships between plasma 25(OH)D concentration and clamp measured in vivo insulin sensitivity, first-phase insulin, and the DI, i.e., β -cell function relative to insulin sensitivity. In evaluating the relationship of 25(OH)D to parameters of glucose homeostasis, it is imperative that sensitive assessment of body composition and body fat topography be performed, to tease out obesity-modulated versus independent relationships, since lower concentrations of 25(OH)D are associated with higher total and abdominal adiposity (13), a strong determinant of insulin sensitivity and secretion.

In agreement with our current findings, the positive association between 25(OH)D and insulin sensitivity, measured by hyperinsulinemic-euglycemic clamp, in nondiabetic obese adults ($n = 39$, mean age of 41.4 years) lost its significance when adjusted for BMI (12). In a limited number of black ($n = 25$) and white ($n = 25$) women, Alvarez et al. (10) found 25(OH)D and parathyroid hormone to be independent predictors of whole body insulin sensitivity index, assessed by the intravenous glucose tolerance test, after adjustments for age, race, and VAT assessed by CT scan. The contrast between their findings and ours may be because of their limited number of subjects; the wider age range of the participants in their study (mean age [SD]: 38.2 $\pm$ 13.1 years), which was limited to women only; and the differences in the methods for assessment of insulin sensitivity. Chiu et al. (11) showed an independent positive association between serum 25(OH)D and insulin sensitivity index from the hyperglycemic clamp in a cohort of glucose-tolerant multiethnic (Asian American [$n = 34$], African American [$n = 11$], white [$n = 54$], and Mexican American [$n = 27$]) young adults after adjusting for BMI and other relevant covariates (age, sex, ethnicity, waist-to-hip ratio, and systolic and diastolic blood pressure). However, they did not have direct measures of body composition or abdominal adiposity, which are known to differ among different ethnicities (18).

To our knowledge, there are no published pediatric data regarding the relationship between 25(OH)D and clamp-derived measures of in vivo insulin sensitivity and β -cell function relative to insulin sensitivity. Moreover, the reported relationships between 25(OH)D and parameters of

glucose homeostasis, assessed by fasting surrogate indices of insulin sensitivity, contrast widely among studies in both children (4,22,23) and adults (2,9,24–26) and are often confounded by adiposity. The differences between these studies and ours may stem from methodological differences, clamp versus fasting or oral glucose tolerance test–derived indices of insulin sensitivity, with the former being the gold standard, BMI versus accurate assessments of total and abdominal adiposity, study population, geographic differences, ranges of BMI investigated (from normal to obese in our case), and measurements made under research-controlled inpatient conditions, in our case and free living conditions in others.

Lack of information regarding dietary intake of vitamin D and calcium, sunlight exposure, skin pigmentation, parathyroid hormone, physical activity and dietary intake, and overrepresentation of obese youth are some of the limitations of our data. Our findings also may be limited by the fact that very few children were vitamin D sufficient ($n = 19$, 10.4%). However, the percentage of obesity among the vitamin D–sufficient children ($n = 10$, 52.6%) was similar to the entire cohort ($n = 92$, 50.3%). The overrepresentation of recognized risk factors for vitamin D deficiency in our sample (obese [50%], black [46%], pubertal [77%]) and season of assessment [44% winter/spring]) may explain the low percentage of vitamin D–sufficient youth in our study (13). Furthermore, there were no differences between the lowest and the highest quartiles of 25(OH)D for any of the metabolic parameters in whites, and the observed differences in insulin sensitivity and DI in blacks were negated when adjusted for adiposity. The strength(s) of our study are the state of the art assessment of total and abdominal adiposity; in vivo measures of insulin sensitivity and β -cell function relative to sensitivity, the latter has never been investigated in the context of vitamin D; and the appreciable number of healthy volunteer youth.

In conclusion, our data show no independent relationship between plasma 25(OH)D and in vivo insulin sensitivity and β -cell function relative to insulin sensitivity in otherwise healthy black and white youth. It remains to be determined whether similar or different relationships will be found in youth with dysglycemia and whether vitamin D optimization in vitamin D–deficient youth will enhance insulin sensitivity and β -cell function.

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K.R. and J.H. contributed equally; they wrote the manuscript, analyzed the data, and participated in data interpretation together with S.A.A. S.L. conducted analyses of abdominal CT and magnetic resonance. M.F.H. conducted the 25(OH)D assays and provided review of the manuscript. S.A.A. was responsible for the study concept and design, acquisition of data, and the analysis and interpretation of data and obtained funding; provided administrative, technical, and material support, and study supervision; drafted the manuscript; and critically revised the manuscript for important intellectual content. S.A.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final draft of the manuscript.

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